PATENT SPECIFICATION

NO DRAWINGS

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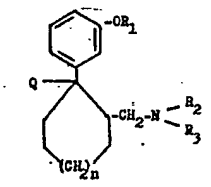
COMPLETE SPECIFICATION

Phenol Ethers that contain Basic Groups

We, CHEMIE GRUNENTHAL G.M.B.H., of Stolberg im Rheinland, Germany, a Body Corporate, organised under the laws of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to phenol ethers that contain basic groups and to a method of preparing these compounds.

The present invention provides new and valuable compounds of the general formula



I

wherein R_1 represents an alkyl radical containing 1 to 3 carbon atoms or an aralkyl radical, R_2 and R_3 have the same or a different meaning and represent alkyl radicals containing 1 to 6 carbon atoms or aralkyl radicals or together with the nitrogen atom represent a morpholine or pyrrolidine group, and n represents 0, 1, or 2 and Q represents a hydroxy group or chlorine atom, or a hydroxy group esterified with an alkanoic acid with 1 to 4 carbon atoms or salts of these compounds with acids.

The compounds of the general formula I, especially those in which n represents the number 1 and R_2 and R_3 represent methyl radicals, exhibit strong analgesic activities and are in most cases well tolerated by the body. For example, the ED_{50} (that amount of the compound after the application of which 50% of the test animals no longer react to pain) for the hydrochloride of 1-(*m*-methoxyphenyl) 2 - dimethylaminomethyl - cyclohexanol - (1) (in the following referred to as compound A) after oral administration, is 23.5 mg/kg mouse body weight. The LD_{50} (that amount of the compound after the application of which 50% of the animals die) of compound A after oral administration, is 395.0 mg/kg mouse body weight. Moreover, the compounds of formula I possess very good antitussive properties, e.g. upon intravenously administration, 2.5 mg of compound A per kg cat body weight cause inhibition of 75% of the mechanically provoked cough reflex of the narcotised cat. This cough reflex is inhibited to a degree of 63% by intravenous application of 2.5 mg of the hydrochloride of 1-(*m*-methoxyphenyl) - 2 - pyrrolidinomethylcyclohexanol - (1) per kg cat body weight, to a degree of 65% by application of 1 mg of the hydrochloride of 1 - (*m* - benzyloxyphenyl)- 2 - pyrrolidinomethyl - cyclohexanol - (1) per kg cat body weight and to a degree of 100% by 2.5 mg of the hydrochloride of 1 - (*m* - methoxyphenyl) - 2 - [N - methyl - N - (β - phenylethyl) - amino - methyl] - cyclohexanol-(1) per kg cat body weight. Compounds with a more or less similar structure, e.g. 1 - (*p* - methoxyphenyl) - 2 - dimethylaminomethyl-cyclohexanol-(1) (compound B) or 1-(*m*-methoxyphenyl)-2-piperidinomethylcyclohexanol-(1) (compound C) are known. The ED_{50} of these compounds, however, on oral administration for testing the analgesic properties, amounts to more than 100 mg/kg mouse, which is especially unsatisfactory with respect to compound C, because, after application of this compound in an

[P

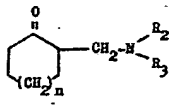
amount of 200 mg/kg mouse, toxic reactions occur (two of ten animals die after being treated with this amount of compound C). Intravenous application of 2.5 mg/kg cat of compound B does not influence the mechanically provoked cough reflex of the narcotised cat. The same amount of compound C inhibits only 38% of the cough reflex.

The alicylic ring in the compounds of formula I contains two carbon atoms each bearing four different substituents. This configuration provides cis-trans-isomerism and the isomers can be resolved into optically active forms by methods known *per se*.

The cis-trans-isomers may, for instance, be separated from each other for instance by distillation of the free bases or by recrystallisation of salts.

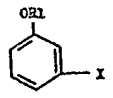
The pharmacological data given above were obtained with mixtures of the different isomers of the compounds, the mixtures being obtained by the synthetic route described below.

The new compounds of formula I are obtained by reacting a compound of the general formula



II

wherein R_2, R_3 and n have the meanings indicated above with a compound of the general formula



III

wherein R_1 has the meaning as indicated above and wherein X represents a lithium atom or the group MgHal in which Hal represents a halogen atom, in presence of an ether which preferably is of the cyclic type and hydrolysing the intermediate thus obtained to give the compounds of formula I, which then may be transformed into salts with acids and/or into esters with alkanoic acids with 1 to 4 carbon atoms.

For esterification with the lower alkanoic acids the compounds of formula I are preferably reacted with halides or anhydrides of these acids.

The reaction of the compounds of the formula II with the compounds of the formula III is preferably carried out at temperatures from −50 to +100°C. To hydrolyse the intermediates, the reaction mixture is treated, preferably while cooling, with water which may contain ammonium salts or with diluted acids

Compounds of the formula I, in which Q represents a chlorine atom, may be prepared by known methods from the tertiary alcohols of the same formula wherein Q represents a hydroxy group, for instance by treating the alcohol with an acidic chlorinating agent, such as thionyl chloride. The following examples serve as further explanation of the invention. Melting and boiling points are uncorrected.

EXAMPLE I

5 g. of magnesium turnings are treated while stirring with a mixture of 37.4 g of *m*-bromoanisole and 160 ml. of absolute tetrahydrofuran at such a rate that the reaction mixture boils gently because of the heat produced by the immediately starting reaction. Thereafter, the reaction mixture is boiled under reflux while stirring until all the magnesium dissolves. The reaction mixture is cooled to 0 to −10°C. and then a mixture of 23.25 g of 2-dimethylaminomethyl-cyclohexanone and 45 ml. of absolute tetrahydrofuran is added dropwise. The resulting mixture is stirred for 4 hours at room temperature and then poured, while stirring slowly, into a mixture of 25 g. of ammonium chloride, 50 ml. of water and 50 g. of ice. The layers are separated and the aqueous layer is extraced twice with 50 ml. portions of ether. The organic layers are combined, dried with sodium sulphate and evaporated. The residue distilled, and 1-(*m*-methoxyphenyl)-2 - dimethylaminomethyl - cyclohexanol - (1), boiling point at 0.6 mm Hg: 138—140° C., is obtained in a yield of 78.6% of theoretical. The hydrochloride obtained from the product e.g. by dissolving in ether and treating with dry hydrogen chloride, melts at 168—175°C. By recrystallisation from moist dioxan this hydrochloride is separated into isomers melting at 162—163° and 175—177° C., respectively. Heating the mixture of the isomers with acetic anhydride provides the hydrochloride of 1-(*m*-methoxyphenyl)-1-acetoxy - 2 - dimethylaminomethyl - cyclohexane, m.p. 150—155°C.

EXAMPLE 2

Following the method described in Example 1 but using 2.5 g. of magnesium turnings, 18.7 g of *m*-bromoanisole dissolved in 80 ml. of absolute tetrahydrofuran and 12.7 g. of 2 - dimethyl - aminomethyl - cycloheptanone - dissolved in 25 ml. of absolute tetrahydrofuran 1 - (*m* - methoxyphenyl)-2 - dimethylaminomethyl - cycloheptanol - (1) b.p./0.003 Hg 125°C. is obtained in a yield of 73.8%. The hydrochloride melts at 177—181°C.

In the same manner, reaction of *m*-methoxy-

phenyl magnesium bromide with the appropriate basic ketones provides the following compounds

a) 1 - (*m* - methoxyphenyl) - 2 - morpholinomethyl - cyclohexanol - (1), boiling point (0.02 mm Hg) 182—183°C., yield 43.7%, melting point of the hydrochloride 231—233° C.

b) 1 - (*m* - methoxyphenyl) - 2 - pyrrolidinomethyl - cyclohexanol - (1), boiling point (0.15 mm Hg) 145 — 147°C. yield 55.5%, melting point of the hydrochloride 174—178°C.

c) 1 - (*m* - methoxyphenyl - 2 - [N - methyl - N - (β - phenylethyl) - amino - methyl] - cyclohexanol - (1), boiling point (0.006 mm Hg.) 167°C., yield 56.7%.

EXAMPLE 3

5 g. of magnesium turnings are treated while stirring with a solution of 1 ml. of ethyl bromide in 15 ml. of absolute tetrahydrofuran. To a warm reaction mixture, is added a solution of 39.5 g. of *m*-bromophenylbenzyl ether in 150 ml. of absolute tetrahydrofuran at such a rate that the mixture boils gently. After boiling under reflux for one further hour, the mixture is chilled to 0 to −10°C. and at this temperature is treated dropwise while stirring with a solution of 23.3 g. of 2-dimethylaminomethylcyclohexanone in 45 ml. of absolute tetrahydrofuran. The reaction mixture is stirred for 4 further hours at room temperature and then is poured slowly into a stirred mixture of 25 g. of ammonium chloride, 50 ml. of water and 50 g. of ice. The layers are separated, the aqueous layer is extracted twice with 50 ml. portions of ether. The combined organic layers are dried with sodium sulphate and evaporated. Distillation of the residue yields 1-(*m*-benzyloxy phenyl) - 2 - dimethylaminomethyl - cyclohexanol-(1), b.p./0.003 mm Hg 156—160°C. Yield 61% of theoretical. The hydrochloride of this compound melts at 141—143°C. Treatment of this hydrochloride with thionyl chloride provides the hydrochloride of 1-(*m*-benzyloxyphenyl) - 1 - chloro - 2 - dimethylaminomethyl - cyclohexane melting, after recrystallisation from ethanol/ether, at 150—151°C.

In the same manner reaction of *m*-benzyloxyphenyl magnesium bromide with the appropriate basic ketones provides the following compounds:

a) 1 (*m*-benzyloxyphenyl - 2 - dimethyl aminomethyl - cycloheptanol - (1), boiling point (0.004 mm Hg) 167—172°C. yield 45.3%, melting point of the hydrochloride 140—143°C. Treatment with thionyl chloride yields the hydrochloride of 1-(*m*-benzyloxyphenyl) - 1 - chloro - 2 - dimethylaminomethyl-cycloheptane, melting at 124—125°C.

b) 1 - (*m* - benzyloxyphenyl - 2 - pyrrolidinomethyl - cyclohexanol - (1), boiling point (0.0002 mm Hg) 175—178°C., yield 27.4%, melting point of the hydrochloride 171—173°C.

c) 1 - (*m* - benzyloxypheny) - 2 - [N - methyl - N - (β - phenylethyl) - aminomethyl] - cyclohexanol - (1), boiling point (0.001 mm Hg) 220—221°C., yield 46.6%, melting point of the hydrochloride 173—175°C.

d) 1 - (*m* - benzyloxyphenyl) - 2 - (N - methyl - N - benzylaminomethyl) - cyclohexanol - (1), boiling point (0.001 mm Hg) 208—210°C., yield 40.1%, melting point of the hydrochloride 188—190°C.

e) 1 - (*m* - benzyloxyphenyl) - 2 - morpholinomethyl - cyclopentanol - (1), boiling point (0.007 mm Hg) 200—205°C., yield 43.6%, melting point of the hydrochloride 169—170°C.

EXAMPLE 4

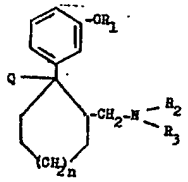
2.8 g. of lithium are added in small pieces, to 150 ml. of absolute ether, under atmosphere of nitrogen, followed, while being stirred, by a few ml. of a solution of 27.5 g. of butyl bromide in 50 ml. of absolute ether. When reaction has started, the mixture is chilled to −10°C. and the remainder of the solution of butyl bromide is added dropwise. The reaction mixture is stirred for 2 hours at 0 to to +10°C. and then chilled to −40 to −50°C. A solution of 39.5 g. of *m*-bromophenyl benzyl ether in a mixture of 60 ml. of absolute ether and 90 ml. of absolute tetrahydrofuran is added slowly while stirring and then a solution of 23.3 g. of 2-dimethylaminomethyl-cyclohexanone in 45 ml. of absolute ether is added dropwise. The reaction mixture is stirred for 2 hours at −40°C., the temperature is then allowed to rise slowly to room temperature. The reaction mixture is worked up in the same manner as described in Examples 1 and 3 giving the same product as in Example 3 in a yield of 49.1%.

EXAMPLE 5

The procedure is the same as in Example 1. There are used, however, 5 g. of magnesium turnings, 40.2 g. of *m*-ethoxybromobenzene dissolved in 160 ml. of absolute tetrahydrofuran and 23.3 g. of 2-dimethylaminomethylcyclohexanone dissolved in 45 ml. of absolute tetrahydrofuran. This provides 1-(*m*-ethoxyphenyl) - 2 - dimethylaminomethyl - cyclohexanol - (1), b.p./0.02 mm Hg. 134—135°C. in a yield of 62.6%. Melting point of the hydrochloride, 170—175°C.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



I

wherein R_1 represents an alkyl radical containing 1 to 3 carbon atoms or an aralkyl radical, R_2 and R_3 have the same or a different meaning and represent alkyl radicals containing 1 to 6 carbon atoms or aralkyl radicals or together with the nitrogen atom represent a morpholine or pyrrolidine group, n represents 0, 1, or 2 and Q represents a hydroxy group or chlorine atom, or a hydroxy group esterified with an alkanoic acid with 1 to 4 carbon atoms or salts of these compounds with acids.

2. 1 - (*m* - methoxyphenyl) - 2 - dimethyl - aminomethyl - cyclohexanol - (1).

3. 1 - (*m* - methoxyphenyl) - 2 - dimethyl - aminomethyl - cycloheptanol - (1).

4. 1 (*m* - methoxyphenyl) - 2 - morpholinomethyl - cyclohexanol - (1).

5. 1 - (*m* - methoxyphenyl) - 2 - pyrrolidinomethyl - cyclohexanol - (1).

6. 1 - (*m* - methoxyphenyl) - 2 - [N - methyl - N (*β* - phenylethyl) - amino methyl] - cyclohexanol-(1).

7. 1 - (*m* - benzyloxyphenyl) - 2 - dimethyl-aminomethyl - cyclohexanol - (1).

8. 1 - (*m* - benzyloxyphenyl) - 1 - chloro - 2 - dimethylaminomethyl - cyclohexane.

9. 1 - (*m* - benzyloxyphenyl) - 2 - dimethylaminomethyl - cycloheptanol - (1).

10. 1 - (*m* - benzyloxyphenyl) - 1 - chloro - 2 - dimethylamino - methyl - cycloheptane.

11. 1 - (*m* - benzyloxyphenyl) - 2 - pyrrolidinomethyl - cyclohexanol - (1).

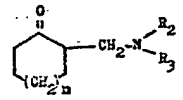
12 1 - (*m* - benzyloxyphenyl) - 2 - [N - methyl - N - (*β* - phenylethyl) - aminomethyl] - cyclohexanol - (1).

13. 1 - (*m* - benzyloxyphenyl) - 2 - (N - methyl - N - benzylamino - methyl) - cyclohexanol - (1).

14. 1 - (*m* - benzyloxyphenyl) - 2 - morpholinomethyl - cyclopentanol - (1).

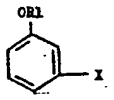
15. 1 - (*m* - ethoxyphenyl) - 2 - dimethyl-aminomethyl - cyclohexanol - (1).

16. A process for the preparation of compounds as claimed in claim 1 wherein Q represents a hydroxyl group which comprises reacting a compound of the general formula



II

wherein R_2, R_3 and n have the meanings indicated in claim 1 with a compound of the general formula



III

wherein R_1 has the meaning indicated in claim 1 and X represents a lithium atom or the group MgHal in which Hal represents a halogen atom in the presence of an ether, hydrolysing the intermediate thus obtained and, if desired, esterifying the compounds of formula I thus obtained with alkanoic acids with 1 to 4 carbon atoms and/or transforming these compounds into salts with acids.

17. A process as claimed in claim 16 wherein the temperature is from −50 to +100°C.

18. A process as claimed in claim 16 substantially as described with reference to any of the Examples.

19. A process for the preparation of compounds as claimed in claim 1 wherein Q represents a chlorine atom which comprises treating compounds of the formula I wherein Q represents a hydroxy group with an acidic chlorinating agent.

20. Compounds of the formula I when prepared by a process claimed in any of claims 16, 17, 18 or 19.

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